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DECLARATION OF JAMES R. SCHNEIDER, M.D. UNDER 37 C.F.R. § 1.132		
	Attorney Docket No.	SNDR-001CIP
	Confirmation No.	5537
	First Named Inventor	SCHNEIDER, JAMES R.
	Application Number	09/307,956
	Filing Date	May 10, 1999
	Group Art Unit	3738
	Examiner Name	David J. Isabella
	Title: "PRESERVED INPLANTABLE VESSEL DERIVED FROM A HUMAN UMBILICAL CORD OR PLACENTA"	

Dear Sir:

1. I, James R. Schneider, M.D. declare and say I am a resident of the State of California.

2. I hold a M.D. degree which I received from University of Iowa. I also hold a Bachelor's degree in Sociology/Psychology which I received from Drake University.

3. I am the inventor of the claimed invention in the above-referenced patent application, which for convenience I refer to as the "Application". The claims are directed to preserved vessels and vascular grafts comprising preserved vessels, where the preserved vessels are isolated from a human umbilical cord or human placenta. In addition, the claims require the preserved vessels or vascular grafts be "suitable for implantation in an adult human".

4. I have reviewed the Office Action mailed January 29, 2007 in the above-referenced application. For convenience I will refer to this document as the "Office Action". I understand that the claims are variously rejected as being "obvious" based on the following combination of references, each of which I have read:

   a. Pratt et al. (Laryngoscope 1986 96(6):625-9; 29th Ann. Meeting of Amer Society for Head and Neck Surgery) ("Pratt"), Dardik et al. (US 3,894,530) ("Dardik"), and McDonald et a. (US 6,090,136; "McDonald") (Claims 27-37 and 38-44);

   b. Dardik and McDonald (Claim 53); and

   c. Pratt, Dardik, McDonald, Lau et al. (US 5,876,432) ("Lau") and Chin et al. (US 5,800,540) ("Chin") (Claims 35-37 and 45-47); and

5. I understand that all claims in the Application recite that the graft or preserved vessel be "suitable for implantation in an adult human". In order to be so suitable, such a preserved vessel, and the graft comprising the preserved vessel, would have to perform its function under the conditions present in the environment in an adult human following implantation. Examples of desirable characteristics that would make a graft or preserved vessel "suitable for implantation in an adult human" include the ability to withstand blood pressure in an adult human.

6. Vessels of human placenta and umbilical cord are quite delicate. Because the vessels are delicate, one in the field of vascular surgery would be discouraged from using such vessels generally and particularly from use of preserved, isolated human umbilical cord or placental vessels that are prepared by direct freeze-drying without chemical denaturing. Below I provide some examples of reasons why this would be the case.

7. Umbilical cord vessels are surrounded by a protective sheath of tissue that prevents damage or collapse of the vessels. The cord sheath permits flexibility longitudinally, but does not permit "sideways" expansion. It does not permit

longitudinal stretching, but can be bent, even so as to result in a knot. In addition, Wharton's jelly, a mucoid connective tissue with a collagen meshwork, surrounds the umbilical vessels in the cord, further supports these vessels and protections them from compression. When compressed, the jelly becomes more rigid, if the cord is being compressed from external pressure and also when umbilical vessel pulsations expand the umbilical vessel. The jelly helps propagate the pulse through its support of the vessel wall. See, for example, pages 3 and 8-10 of the attached Exhibit, which are taken from reference texts describing some of the protective functions of the cord sheath and Wharton's jelly.

8. On page 9 of the Exhibit, the reference text states that umbilical vessels that have lost protection by Wharton's jelly are more vulnerable to trauma and disruption. On page 10 of the Exhibit, the reference text indicates that in situations where the umbilical cord vessels are separate from the cord substance, they lose protection afforded by Wharton's jelly and are prone to thrombosis and injury. These observations would discourage one in the vascular surgery field from isolating vessels from umbilical cord for use as grafts.

9. Isolated umbilical vessels that lack the protection of the cord sheath and the support of the Wharton's jelly cannot be assumed to be able to function without that support.

10. Umbilical vessels allow for transudation of fluids. See, for example, Exhibit pages 4 and 5, which provide reference texts discussing this feature. Vessels that allow for transudation of fluids would be expected to have walls that are structurally compromised or weaker compared to vessels such as adult vessels that do not allow for transudation of fluids.

The structure of human umbilical vessels and human placental vessels differs from that of adult human vessels. The table set out at page 11 of the Exhibit provides a comparison of the structures of these vessels.

11. As summarized in the table on page 11 of the Exhibit, there are significant structural differences between human umbilical vessels (arteries and veins) and human adult vessels (arteries and veins). The asterisks (*) in the table on page 11 of the Exhibit denote the importance of the intima basal lamina and the media smooth muscle layers, both of which layers provide vessel strength and also propagate the pulse. In addition, the lack of neural fibers in human umbilical vessels and in human placental vessels, and thus the lack of neural connections to the smooth muscular, would suggest to one in the field of vascular surgery that the umbilical cord vessel walls and placental vessel walls would be too thin and weak to be suitable as a graft for implantation in an adult human. In addition, human placental vessels have only Type I collagen, which is structurally weaker than Type II collagen. Thus there are significant structural differences between human umbilical cord vessels and human adult vessels, and significant structural differences between human placental vessels and human adult vessels (arteries and veins).

12. In view of the significant structural differences between human umbilical vessels and adult human vessels, the significant structural differences between human placental vessels and adult human vessels, and further in view of the susceptibility of isolated human umbilical vessels (which lack the protection afforded by the umbilical cord sheath and Wharton's jelly) to compression and damage, one in the field of vascular surgery would not look to umbilical cord vessels or to human placental vessels as a source for making a preserved, isolated vessel prepared by directly lyophilizing the isolated vessel (without chemical denaturing) to produce a vessel that, following rehydration, would be suitable for implantation in an adult human.

13. Human umbilical cord and placental vessels are normally only subjected to fetal blood pressure. Fetal blood pressure is usually in the range of about 60/25 mmHg. In contrast, blood pressure in a healthy adult is about 140/80 mmHg.

14. Placental and umbilical cord vessels in nature are thus subjected to less than about half of the pressure to which adult vessels are subjected. Moreover, blood pressure in adults with hypertension or malignant hypertension (those who would likely receive an endovascular graft) is even higher – about 160/90 and 180/120, respectively.

15. Thus, in order for a preserved vessel, or graft comprising a preserved vessel, to be "suitable for implantation in an adult human", the preserved vessel must be able to withstand blood pressures

16. I earlier submitted my declaration dated January 28, 2005, to which I will refer as the "2005 Declaration". As I stated in my 2005 Declaration, it could not have been predicted that the integrity of placental or umbilical cord vessels would be maintained after freeze-drying. Similarly, there was no reasonable expectation that freeze-dried human placental or human umbilical cord vessels would be "suitable for implantation in a human adult", specifically that these freeze-dried vessels could withstand at least twice or more the blood pressure than that to which the fresh tissue is subjected in nature. However, in my 2005 Declaration I provided evidence to support the assertion that both human umbilical cord vessels and human placental vessels that were directly freeze-dried (without chemical denaturing) then later reconstituted with saline were suitable for implantation in an adult human. Specifically, the freeze-dried human umbilical vessels following rehydration withstood a steady 120 mmHg pressure, as well as pulsed pressure 120/80 mmHg, as well as pressure at 160/120 mmHg pressure. There was no aneurysm formation or vessel wall rupture. (See 2005 Declaration, pars. 12-1 and 27-36).

THE DARDIK REFERENCE

17. In reviewing Dardik, I noted that the reference instructs one to store the entire umbilical cord, and no where instructs one to isolate a vessel from the umbilical cord, then to preserve it by direct lyophilization without chemical denaturing. For example, the discussion at col. 1, line 62 to col. 2, line 9 only discusses storage of the entire umbilical cord. I particularly noted that the reference provides a single working example, which states the following at col. 2, line 49 to col. 3, line 22

> During preparation of the abdominal aorta of the baboon, another investigator had taken the umbilical cord of an infant (human) that had been born two hours prior to the surgical intervention of the baboon. The cord had been delivered and taken in its entirety and transported in sterile saline solution, packed in ice. The purpose of freezing the umbilical cord in ice was to prevent any further decomposition of the cord structure. The cord, prior to insertion, was washed and irrigated numerous times with sterile Collins solution with antibiotics, in this particular instance, 1 percent cephalosporin solution and 25,000 units of bacitracin per liter of solution. The blood was thoroughly washed out from within the vessels of the cord and the cord was also irrigated with a 1 percent heparin anticoagulant solution. Following this thorough cleansing of the cord, one end of the umbilical vein within the cord which was to be used as the transplant was clamped with a clamp and through the

> other end a red rubber catheter, No. 14 French, was introduced and the vein was distended. At this point a suitable segment of umbilical graft, approximately 5 centimeters in length, was selected for excision. This segment of cord was then sterilely handled and placed into the operating field. At this point the animal was heparinized with 2,500 units of aqueous heparin given intravenously. The abdominal aorta was then clamped proximally and distally to the segment to be resected. A segment of approximately 3 centimeters in length was resected from the abdominal aorta and an end-to-end anastomosis was performed between host aorta and donor umbilical vein, first using continuous 6-0 prolene suture which is a nylon monofilament suture. The distal anastomosis was then performed following flushing of the aorta to rid it of any clot material and debris. Following completion of anastomosis the distal and then the proximal clamps were removed. It was noted that there was no bleeding between the interstices of the sutures, which is unusual, and is felt to be due to the strength and self-sealing gelatinous qualities of the cord structure.

(underlining added)

18. In the only working example provided, Dardik instructs that the vein used in the anastomosis is still in the umbilical cord segment and is not removed and/or isolated from the umbilical cord segment *prior to* performing the anastomosis at the time of implantation. Dardik does not instruct or suggest isolating an umbilical cord vessel and preserving it separately from the umbilical cord. Instead, Dardik instructs one to use the vessel as part of a "suitable segment of umbilical graft" or "segment of cord".

19. In addition, Dardik points to the "strength and self-sealing gelatinous qualities of the cord structure" to be due to the "unusual" feature that there was "no bleeding between the interstices of the sutures". This would instruct one *not* to isolate vessels separate from the umbilical cord and preserve the *isolated* vessel, as such a method would not take advantage of the "strength and self-sealing gelatinous qualities of the cord structure", which would be provided by the Wharton's jelly.

THE PRATT 1987 AND PRATT 1986 REFERENCES

20. In my 2005 Declaration I also commented on the statement in the Pratt reference 29th Ann. Meeting of Amer Society for Head and Neck Surgery ("Pratt 1987") of which I am a co-author. I am also a co-author of Laryngoscope 1986 96(6):625-9 ("Pratt 1986").

21. The Office Action points Pratt 1986 and Pratt 1987 as suggesting that freeze-dried human placental vessels should be explored as microarterial allografts.

22. Specifically, Pratt 1987 states at page 11, last full paragraph:

> With the limitations of the present study notwithstanding, this new microvascular technique shows promise. Eventually, it is anticipated that freeze-dried placental or donor vessels could be used in clinical trials if future preliminary laboratory studies in rabbits and larger animals are successful.

23. Pratt 1986 states at page 628, col. 1:

> A good topic for further investigation would be the study of freeze-dried human placental vessels used as microarterial allografts. Success with such an investigation would provide a readily available source of vascular grafts without the inconvenience and additional morbidity associated with harvesting autogenous veins.

24. These statements in Pratt 1987 and Pratt 1986 are merely wishful statements. At best it is a suggestion to try use of freeze-dried human placental vessels. There is nothing in either of the Pratt 1987 or the Pratt 1986 references, or in the literature at the time of filing of my application on August 10, 1998, that provided certainty that a freeze-dried human placental vessel would be, following rehydration, suitable for implantation in a human adult, e.g., would have sufficient integrity to withstand blood

pressure of a non-fetal human (e.g., a human adult). In addition, both Pratt 1987 and Pratt 1986 are silent as to use of freeze-dried, isolated vessels from human umbilical cord would be, following rehydration, suitable for implantation in an adult human. As co-author of both of these references, I believe I am well-positioned to provide my opinion as to how these references would be viewed by the someone in my field.

25. In addition, Pratt 1986 also includes statements about the use of freeze-dried arteries from rats versus the use of freeze-dried veins. At page 628, Pratt 1986 compares the results of a prior study (Pratt et al. 1985 Microsurgery 6:211-218; "Pratt 1985") using freeze-dried veins from donor rats in allografts in recipient rats. Pratt 1986 states at page 628, col. 2:

> The freeze-dried arteries were much easier to implant due to the natural rigidity in the walls, which helped to keep the lumens open during anastomosis. The walls of the freeze-dried veins readily collapsed, making anastomosis technically difficult and time consuming. There were no aneurysmal dilatations found with freeze-dried arteries as was previously reported with freeze-dried veins. All of these observations suggest that the freeze-dried microarterial allograft may be more clinically applicable than the freeze-dried microvenous allograft.

26. This statement in Pratt 1986 makes it apparent that results differed significantly between use of freeze-dried rat veins and use of freeze-dried rat arteries. Given that success in using freeze-direct adult rat arteries did not necessarily predict success with freeze-dried adult rat vein, one would not expect that success with freeze-dried adult rat arteries would predict success with either freeze-dried human placental vessels or with freeze-dried human umbilical cord vessels.

27. I, James R. Schneider, M.D., hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

June 28, 2007
Date

James R. Schneider, M.D.
James R. Schneider, M.D.

Enclosure: Exhibit 1

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Kurt Benirschke, MD
Peter Kaufmann, MD
Rebecca Baergen, MD

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In general, the amnion of the cord is structurally similar to that described in the membranes; and there are no indications that this is different for its basic functions (see Chapter 11). In contrast to the amnion that covers the chorionic surface of the placenta, however, and that of the membranes where it is easily detached, the amnion of the cord grows firmly into the central connective tissue core. It cannot be dislodged.

Wharton's Jelly

The connective tissue of the cord, or Wharton's jelly, is derived from the extraembryonic mesoblast. McKay et al. (1955) referred to this jelly-like material of the exocoelom as a "thixotropic gel" because it liquefies when touched (see also Bacsich & Riddell, 1945). The incorporation of this mesenchyme into the cord substance and the subamnionic layers probably accounts for their mucoid and compressible structures. The importance of this faculty was stressed by Reynolds (1952). He likened the compressed (by distended fetal vessels) Wharton's jelly to erectile tissue. It is clearly true that a filled umbilical cord is a relatively firm, rigid structure and that, with expansion and contraction of the vasculature, its thickness and turgidity vary. Strong (1997a) reviewed this protective function of Wharton's jelly. This jelly is composed of a ground substance of open-chain polysaccharides (hyaluronic acid: Graumann, 1964; carbohydrates with glycosyl and mannosyl groups: Yamada & Shimizu, 1976), distributed in a fine network of microfibrils. Immunohistochemically, the interstitial collagens types I, III, and VI, as well as the basal lamina molecules collagen type IV, laminin, and heparan sulfate were found (Nanaev et al., 1992, 1997). Immunoreactivities for these extracellular matrix molecules were accumulated around cleft-like territories ("stromal clefts") in Wharton's jelly; the stromal clefts themselves were occupied by homogeneous ground substance, which was devoid of collagens and basal lamina molecules but probably contained ample proteoglycans. These fiber-free stromal clefts must not be misunderstood as lymphatic vessels that exist neither in the cord nor in the placenta.

Wharton's jelly contains evenly distributed spindle-shaped fibroblasts with long extensions (Parry, 1970) and numerous mast cells. These cells can be stained selectively, surround the vessels densely, and are also found underneath the cord surface (Moore, 1956). Electron microscopic and immunohistochemical studies by Takechi and coworkers (1993) revealed that the stromal cells embedded into the collagen meshwork were myofibroblasts rather than typical fibroblasts. Myofibroblasts are fiber-producing cells that have contractile properties similar to those of smooth muscle cells. These data were supported and further extended by Nanaev and coworkers (1997). According to these authors, the stromal cells of Wharton's jelly depending on their location within the cord, show different degrees of differentiation from mesenchymal cells to myofibroblasts:

- The most immature, still proliferating cells are located close to the amnionic surface. These undifferentiated cells very likely correspond to cells isolated from Wharton's jelly, which proliferate well in vitro and contain stem cells that differentiate into neurons and glia (Mitchell et al., 2003).
- With increasing distance of the amnionic surface, the stromal cells acquire cytoskeletal features of contractile cells, including desmin, α-smooth muscle actin and partly also γ-smooth muscle actin.
- In close proximity to the umbilical vessels highly differentiated myofibroblasts expressing additionally smooth muscle myosin were found.

The myofibroblasts and their less differentiated precursors line the jelly-filled, stromal clefts of Wharton's jelly (Nanaev et al., 1997). The authors speculated that jelly-filled stromal spaces together with the surrounding meshwork of contractile cells serve as a mechanism for turgor regulation of the cord, avoiding compression of umbilical veins and counteracting bending of the cord.

There are surprisingly few macrophages in the umbilical cord. Even when the cord is deep green due to meconium staining and when meconium-filled macrophages are readily seen in the membranes, only relatively few activated and pigmented macrophages are seen in the cord substance. Similarly, after intrafunicular bleeding, hemosiderin is not formed in situ.

The tensile properties of the cord have been reported by Ghosh et al. (1984). No significant differences in the tensile parameters with respect to the sex of the baby were found, but there was a significant positive correlation between the tensile breaking load and the birth weight of the baby. The average tensile breaking load is

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(Parry & Abramovich, 1972; Las Heras & Haust, 1981) and thus structurally different from the endothelium of the villous vessels. Gebrane-Younes et al. (1986) have given a careful account of the ultrastructure of the endothelium. They described ultrastructural evidence that transudation of fluid through the umbilical vessel walls contributes to the formation of amnionic fluid.

Despite all differences among umbilical and villous endothelium, human umbilical vein-derived endothelial cells (HUVECs) are often used for cell culture as models for "placental endothelium." The findings by Lang et al. (1993) suggested to us that we should be careful with the interpretation of such experiments. The latter authors described considerable differences among umbilical and villous endothelium with respect to cell surface markers and receptors for transferrin and immunoglobulin G (IgG).

Slender endothelial extensions, penetrating the basal lamina, may interdigitate with the neighboring muscle cells and form an endotheliomuscular system (Nikolov & Schiebler, 1973). The arteries possess no internal elastic membrane and have much less elastica in general than other arteries (Boyd & Hamilton, 1970; Nikolov & Schiebler, 1973). The vein, on the other hand, has an elastic subintimal layer (Fig. 12.3). The muscular coat of the arteries consists of a system of crossing spiraled fibers (von Hayek, 1936; Goerttler, 1951; Scheuner, 1964). Desmin-positive smooth muscle cells are largely concentrated on the outer layer of the media (Nanaev et al., 1991). In contrast, the inner media smooth muscle cells are poorly differentiated with few myofilaments (Meyer et al., 1978; Sexton et al., 1996). They hardly can contribute actively to postpartal closure of the cord arteries. The venous muscular coats are thinner than those of the arteries and composed of more separate layers of longitudinal or circular fibers. Media smooth muscle cells of the cord and adjacent chorionic vessels are major placental storage sites for glycogen; only minor quantities were found in the surrounding stromal myofibroblasts. Glycogen levels showed a strong direct correlation with fetal birth weight (Mvumbi et al., 1996).

Cardoso and colleagues (1992) have analyzed the extracellular matrix of isolated umbilical arteries. In general, hyaluronic acid was increased, whereas heparan sulfate and chondroitin 4- and 6-sulfate were reduced in normal umbilical arteries as compared to normal adult systemic arteries. Following hypertension in pregnancy, the total glycosaminoglycan and collagen content of the umbilical arteries were reduced; these changes were unlikely to impair the hemodynamic properties of the cord vessels. Each umbilical vessel is surrounded by crossing bundles of spiraled collagen fibers that form a kind of adventitia. The umbilical vessels of human umbilical cords lack vasa vasorum. Fetuses beyond 20 weeks of gestation, however, have vasa vasorum in the intraabdominal portions of their umbilical arteries (Clarke, 1965).

INNERVATION

There is general agreement about the findings by Spivack (1943) that no nerves traverse the umbilical cord from fetus to placenta, and that the placenta has no neural supply. A number of investigators, however, have since investigated this apparent lack of nerves, and some have come to different conclusions. Thus, Kernbach (1963) studied the amnion with Cajal stains and considered the powdery Nissl substance of extravillous trophoblast cells to represent sympathicoblasts with nerve fibers. He also believed that he had identified nerves in the amnion (Kernbach, 1969). Ten Berge (1963) reviewed the older literature on this topic and found only three authors who claimed to have demonstrated nerves by "persevering techniques." Ten Berge was unable to obtain convincing preparations with a variety of stains. He believed, however, that the responsiveness to oxygen perfusion and a variety of pharmacologic agents argues in favor of innervation. Fox and Jacobson (1969) stained various segments of umbilical cords from abortuses and term placentas with methylene blue and observed fibers in all segments of all cords. The fibers were most easily seen in Wharton's jelly but surrounded and entered the vascular walls. Fox and Jacobson interpreted the fibers to be neural elements. It is possible that these structures relate to the vagal fibers described in embryos by Pearson and Sauter

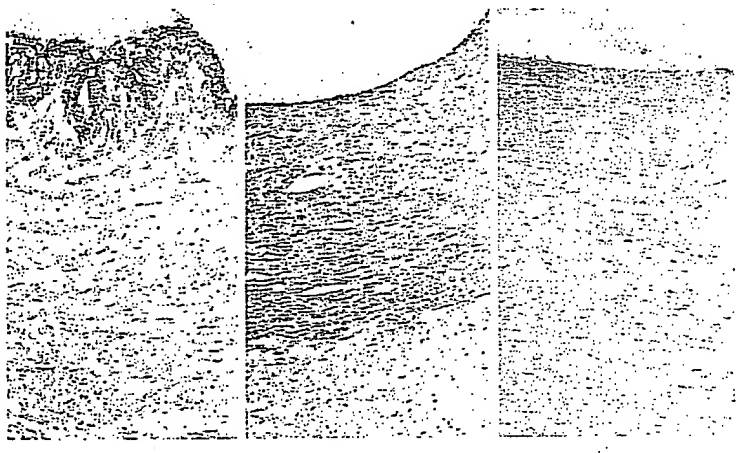

FIGURE 12.3. Umbilical cord sections of a stillborn with necrosis (from thrombosis) of one umbilical artery (right) and a normal artery (middle) and vein (left). In these sections, one may observe the presence of a delicate subendothelial elastica only in the vein at left. von Gieson ×160.

Pathology of the Human Placenta

Third Edition

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With 642 Illustrations

Springer-Verlag
New York Berlin Heidelberg London Paris
Tokyo Hong Kong Barcelona Budapest

the growth of fetal vessels in the first place, and do the false knots merely signify a temporal discrepancy of vascular growth with cord lengthening? Answers to these questions elude us at present.

A completely forgotten notion, the "angle of insertion" (*Insertionswinkel*) to which Hyrtl (1870) tried to draw attention, suggests that one may infer the position held in utero and reflect trophotropic departure of the placenta from its original site of implantation. This angle was between 0° and 90° in the original observations and is clearly variable when one examines placentas. Strassmann (1902) regretted that in his studies on placenta previa he failed to take note of this feature, which might have enhanced his conviction of the etiology.

Strictures

Significant reductions in the size of the umbilical cord are referred to as stricture, torsion, and coarctation. These abnormalities are often found on the abdominal surfaces of macerated fetuses with long, heavily spiraled cords. Javert and Barton (1952) have been depicted this problem in several of their illustrations. One must assume that the fetus has been so active as to have sheared off the blood supply at the site of torsion. In the previous edition of this book we were skeptical about the significance of this lesion and some of the case reports. Since then we have seen many additional cases that have convinced us it is a real phenomenon. One may even see much congestion on one side of the torsion and find thrombi. Because they are often macerated fetuses, the demonstration of thrombi is hampered.

A typical case of cord constriction is shown in Figure 244, and several authors have provided single case reports (King, 1926; Weber, 1963; Quinlan, 1965; Virgilio & Spangler, 1978; Robertson et al., 1981; Glanfield & Watson, 1986). These authors have shown that the phenomenon is not confined to abortions or to the fetal end of the cord. Glanfield and Watson (1986) reported a case with a fresh thrombus at the site of torsion at the twisted placental end of the cord that led to fetal death at 35 weeks' gestation. They also reviewed the sparse literature of this anomaly whose etiology is not known. Nevertheless, Weber (1963) stated that the constriction is rarely reported, although it is not uncommon, and described five cases.

Robertson et al. (1981) surmised that the cause of constriction is a primary deficiency of Wharton's jelly, a true coarctation. These investigators lost two fetuses with this lesion soon after amniocentesis. Hersh and Buchino (1988), who observed two successive deaths in one family due to torsion of the cord, also believed that primary absence of Wharton's jelly is the cause of this lesion. They had previously seen two similar cases in one family and hinted at the possibility that the recurrence risk is greater than what had been thought. There is, of course, normally a gradually diminishing amount of Wharton's jelly near the abdominal surface. It may be for this reason that the stricture is most commonly seen at that site. We have had such a case where with a 64 cm umbilical cord in a stillborn the two umbilical arteries exhibited significant, long-standing degenerative changes at this site. It was the cause of the fetal death.

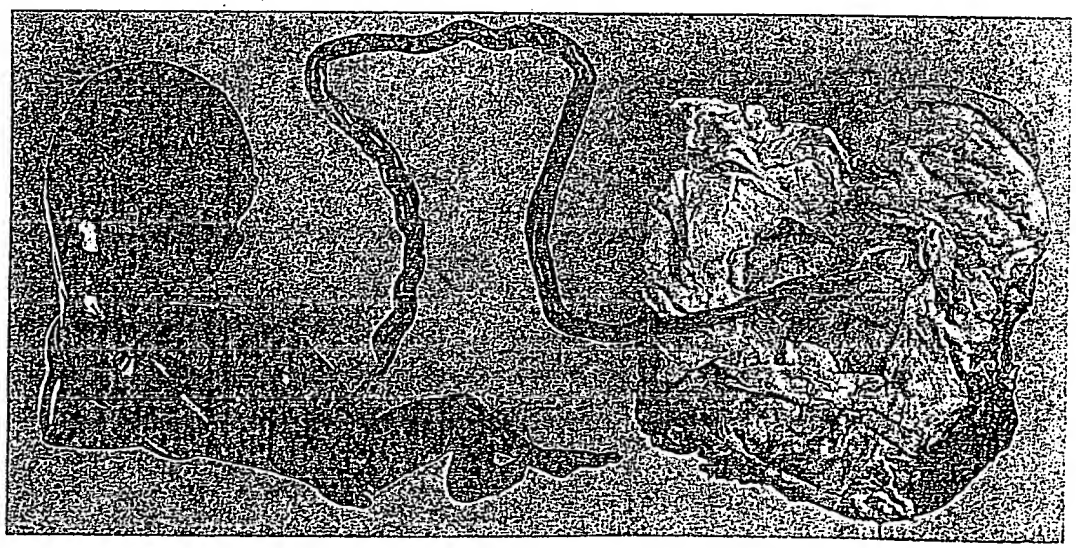

FIGURE 244. Spontaneous abortus at about 14 weeks' gestation. Note the markedly spiraled cord and severe constriction of the cord (coarctation, torsion) near the fetal surface that led to death.

leads to cerebral necrosis (Clapp et al., 1988; Mallard et al., 1992). Gill and collaborators (1993) measured the quantity of jelly in umbilical cord; they found a positive relation to male fetuses, increased prepartum maternal weight, and heavier birth weight.

Excessively thin umbilical cords are abnormal and potential causes of fetal problems. This condition was referred to as the "thin cord syndrome" by Hall (1961). It may involve the entire cord or only portions of the umbilical cord. The latter is seen most often in cases in which the cord has become extremely thinned near the abdominal surface of the fetus due to torsion, so-called coarctation. It frequently leads to fetal death and abortion. In the prototype of abnormally thin cord there is a deficiency of Wharton's jelly, and compression of vessels is a greater possibility than when they are protected. Thin cords occur more often with growth-retarded fetuses and in preeclampsia, but unknown causes exist as well. Labarrere et al. (1985) presented three cases in which Wharton's jelly was deficient, with arteries free next to the umbilical cords and causing fetal demise. Meconium is often present and may be the cause of degenerative changes that are occasionally seen.

Single Umbilical Artery

Single umbilical artery (SUA) is the commonest true congenital anomaly of humans. An enormous literature has been created in efforts to explain its nature and significance. Our files contains more than 80 papers dealing with SUA, and many more are reviewed and critically analyzed in the review articles by Heifetz (1984) and Leung and Robson (1989). These reports can be consulted for all of the relevant literature.

Single umbilical artery was apparently first described by Vesalius. It did not attract further notice until the 40 cases listed by Otto (1830) and the later attention by Hyrtl (1870), who summarized 70 cases in an interesting monograph. Considering its incidence of about 1% in newborns (Heifetz compiled all data and reported there being a 0.63% frequency), it is surprising that its relation to anomalous fetal development was overlooked for so long—until we drew attention to it again (Benirschke & Brown, 1953; Benirschke & Bourne, 1960). Since then, there has been a veritable flood of information on SUA (Table 18). It can now be detected prenatally by ultrasonography (Tortora et al., 1984; Herrmann & Sidiropoulos, 1988), and Jones et al. (1993) made the point that it is unforgivable if it is not ascertained. Among the seven patients of Tortora et al. (1984), four had hydramnios, two were growth-retarded, two died, two survived with anomalies, and three were normal infants. Herrmann and Sidiropoulos (1988) found SUA in four cases and drew attention to the growth retardation of the neonates. The relation of SUA to growth retardation has also been studied by Rolschau (1978). He found that SUA correlated with circumvallation of the placenta, and that marginal cord insertion was moderately well correlated with small placentas and fetuses. Velamentous insertion of the cord, however, had a strong negative effect on fetal and placental weights. Leung and Robson (1989) found SUA in 159 of 56,919 infants. Twins had an incidence of 8.8%, and it was usually the smaller twin who had the anomaly. SUA was associated with diabetes, epilepsy, preeclampsia, antepartum hemorrhage, hydramnios, and oligohydramnios. Anomalies were detected in 44.7% of the associated infants, and other placental abnormalities were found in 16.4%. Because of the frequency of renal anomalies (18.5%) these authors recommended that neonatal renal sonography be performed when SUA is found. Abuhamad et al. (1994) found sonographically that 70% of SUA locates to the left artery and that cytogenetic and complex anomalies were associated with that side. Theirs is the largest prospective series, and they found a 30% associated anomaly incidence.

TABLE 18. Frequency of SUA in various populations.

Series of prospective deliveries	Total	SUA No.	SUA %
Review	332,067	2,099	0.63
Autopsies	18,614	357	1.92
Twin deliveries	1,323	51	3.85
Twin infants	2,399	56	2.33

Data from Heifetz (1984).

Absence of one umbilical artery may occur as aplasia or as the consequence of atrophy of one artery. The latter mechanism is probably more frequent and can be seen to have occurred in many specimens when histological examination is undertaken (Figure 239). Degeneration of one artery occasionally occurs late in pregnancy, but when it took place some time before birth the arterial lumen gradually vanishes, and only a tiny muscular remnant then remains (Figure 240).

The question whether SUA due to "aplasia" has a prognosis different from that due to "atrophy" was examined in a large study by Altshuler et al. (1975). These authors found 19 placentas with SUA among 4,138 consecutive deliveries (0.46%). Altogether they analyzed 48 children with this anomaly and found no significant difference "in congenital malformations or neonatal mortality." The more frequent detection of SUA in term placentas than in placentas of early gestation further supports the view that the etiology involves arterial atrophy. On the other hand, early embryos with SUA have also been seen, and SUA has been observed

thesis is supported by our finding a nuchal cord with fetal death in an otherwise well developed extrauterine (tubal) fetus. The umbilical cord of this fetus was occluded, yet it was clearly stationary.

Prolapse of the cord is associated more often with long cords than with those of normal length. At times this situation has grave prognostic significance for the fetus. Widholm and Nieminen (1963) recorded cord prolapse in 0.41% of 7,500 deliveries with a 13.4% perinatal mortality. This figure is similar to the results published by Brant and Lewis (1966), who urged that a prolapsed cord be kept warm so as to avoid spasm of vessels. A more recent review of the topic was provided by Levy et al. (1984), who found this complication more often in multiparous women. One-half of their study group had fetal malpresentations, one-third had premature onset of labor, and a variety of other abnormal factors were present. Good obstetrical management usually provided a good fetal outcome so long as the fetus was alive on admission. Dildy and Clark (1993) found that cord prolapse occurred in 1 of 275 deliveries, and that the risk was greatest with artificial rupture of membranes with high presenting fetal parts. It has been cautioned that many cases of fatal cord prolapse result from amniotomy, and that some occur after external fetal version (Lehman, 1983). It is now possible to make the diagnosis antenatally with ultrasonography, particularly when malposition and hydramnios suggest this possibility (Lange et al., 1985). A large study on causes of, or associations with, cord prolapse was undertaken by Critchlow et al. (1994). Their findings indicated a high cesarean section rate, 10% mortality, and high prematurity and breech rates; data on the length of the cord were not available. The hemodynamic response with fetal heart rate monitoring has been detailed by Lee and Hon (1963) and is of particular importance for cases with "occult" prolapse. These authors found prompt, marked bradycardia when the umbilical arteries were occluded and believed that it probably resulted from increased fetal blood pressure. This finding has come to be looked at as being pathognomonic for the detection of cord compression during monitored labor. The compressed umbilical cord may show profound pathological changes, such as hemorrhage, and even rupture at the site of compression. It leads occasionally to thrombosis, found when multiple sections are obtained but thrombi ensue more commonly in the surface chorionic vessels. That cord compression may have serious fetal neurological consequences is one of the reasons for taking the "cord compression pattern" of fetal heart monitoring seriously. Its effects on CNS damage has been amply studied in fetal sheep (Mallard et al., 1992). They detected that even short arterial occlusion may cause damage predominantly in the hippocampal area.

Site of Cord Insertion

The umbilical cord normally inserts on the placental tissue itself, more often near or at the center than elsewhere, as shown in Figure 229. In nearly 7% of term placentas it has a marginal insertion, which in the English literature is often referred to as a *Battledore placenta*. In about 1% of placentas the umbilical cord inserts on the membranes, referred to as *velamentous insertion*. Here the umbilical vessels course over the free membranes and, having lost their protection by Wharton's jelly, are more vulnerable to trauma and disruption.

Not only are the sites of insertion variable, the insertion itself may take an abnormal shape: The vessels may branch before the cord comes to the surface of the placenta with the *furcate cord insertion* (Ottow, 1923). At times the cord runs parallel to the placental surface or in the membranes before its vessels branch—the *interposition* (Ottow, 1922). The fetal end of the umbilical cord may also be anomalous, as is found primarily in infants with gastroschisis (short cords) (Figure 226) or with omphaloceles. These conditions can now be diagnosed prenatally and assume a greater importance in management than they did in the past (Didolkar et al., 1981). Some of these anomalies are associated with significant disturbances in fetal growth or during delivery and are thus of importance. Moreover, the formal genesis has interested students of the placenta so they may obtain a better insight into the factors that regulate placental growth. We have seen typical interposition in a case of trisomy 13 associated with a severely malformed fetus and extensive thrombosis of fetal vessels. The umbilical vein of the interposed segment had mural

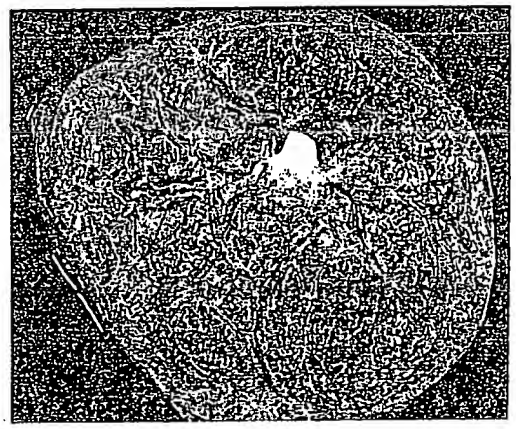

FIGURE 229. Normal term placenta with near-central insertion of the umbilical cord. Note the disperse distribution of the vessels, marginal membranes, and calcified yolk sac remnant (arrow).

thrombosis and old calcifications in the wall; the fetus had intestinal arterial thrombi.

Furcate Cord Insertion

Furcate cord insertion is a rare abnormality in which the umbilical vessels separate from the cord substance prior to reaching the surface of the placenta. They lose the protection afforded by Wharton's jelly and are prone to thrombosis and injury. The condition was first described in three patients by Hyrtl (1870) and received additional attention from Herberz (1938) (six cases) and Swanberg and Wiqvist (1951) (stillborn, hemorrhage). Four of Herberz' cases were associated with normal infants, and much discussion was devoted to its differentiation from velamentous insertion. Kessler (1960) also described fatal hemorrhage associated with this condition and supplied an extensive literature of intrapartum hemorrhage on request. The manner of insertion and the dissociation of vessels from the cord substance are well seen in Figure 230. This placenta was associated with normal outcome. The infant whose placenta is shown in Figure 231, however, was growth-retarded and had low Apgar scores. The furcate and velamentous cords had varices and numerous mural thrombi; many of the placental vessels had degenerations and calcifications in their walls. This case illustrates why the conditions "furcate" and "velamentous" have often posed semantic problems of classification.

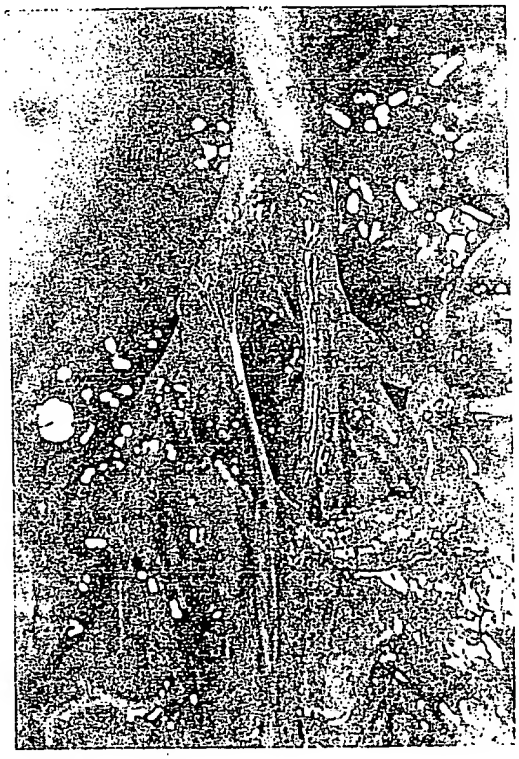

FIGURE 230. Furcate insertion of the umbilical cord. Note that the umbilical vessels leave the protection of Wharton's jelly several centimeters above the cord insertion on the placenta. (Courtesy Dr. W. Tench.)

Velamentous Cord Insertion

Because of its relative frequency and its importance to the course of pregnancy and delivery, membranous insertion of the umbilical cord has been studied by many investigators. Complications include rupture of membranous vessels and vasa previa. Moreover, vasa previa may be compressed during labor and cause fetal distress (Cordero et al., 1993). Velamentously inserted cords are associated with twinning and single umbilical artery (SUA). The incidence of various types of cord insertion varies among numerous reported series because the interpretation of what is truly a marginal or already a velamentous insertion or merely an excessively eccentric one differs in the eyes of the beholder. Nevertheless, Table 16 shows that most observers agree that the frequency of the velamentous insertion is around 1% of singleton term deliveries. The cord may insert reasonably close to the edge of the placenta. This insertion is much more common than the extreme situation, where the cord inserts at the apex of the membranous sac. In the latter configuration the long membranous course of the vessels makes them vulnerable to injury. It should be pointed out, though, that a membranous course of fetal blood vessels is not reserved to velamentous insertion of the cord. Often there are such membranous vessels issuing from marginally inserted cords, and they have the same serious prognosis. Also, membranous fetal vessels are not the same as vasa previa. The latter condition exists only when the membranous vessels course over the internal os uteri, previous (ahead of) to the fetal head during delivery.

Thrombosis of arteries (Figure 232) and veins (Figure 233) have both been seen, and thrombi may be associated with neonatal purpura and fetal death. Hemorrhages arise most commonly from the veins, and they are the most frequent complications of membranous vessels. Hemorrhages may even commence in utero before labor has begun (Bilek et al., 1962). More often they are found when the membranous vessels course over the internal os and are, as "vasa previa," broken by the exiting fetal head or by the obstetrical attendant who ruptures the membranes (Quek & Tan, 1972). Obolensky (1967) provided a description of the differential diagnosis of fetal (versus maternal) blood for such unsuspected vaginal bleeding. The manner by which fetal blood can be distinguished from maternal blood is discussed in greater detail in the discussion on hemorrhage due to placenta previa and in Chapter 17. Exsanguination from ruptured vasa previa can proceed within minutes. We have seen fatalities occur within 3 minutes of disruption through unrecognized velamentous vessels. Experience of successful immediate

TABLE

Layer	Human Adult Artery	Human Adult Vein	Human Umbilical Artery	Human Umbilical Vein	Human Placental Surface Vessel	Human Placental Villous Vessel
Tunica Intima	**(Three layers)**					
	Endothelium endothelial cells	thin endothelium	endothelium	endothelium intimal folds (Valves of Hoboken)	thin endothelium -	thin endothelium -
	Subendothelium smooth muscle collagen	smooth muscle collagen	smooth muscle collagen	smooth muscle collagen	smooth muscle collagen	- -
	Basal Lamina * thick elastic layer	some elastic fibers	elastic fibers	elastic fibers	elastic fibers	-
Tunica Media	* smooth muscle multilayered Type II collagen elastic fibers neural fibers	smooth muscle cells Type II collagen elastic fibers neural fibers	smooth muscle cells Type III collagen elastic fibers -	thin muscle layer Type III collagen elastic fibers -	thin muscle layer Type I collagen elastic fibers -	- Type I collagen - -
Tunica Adventitia	Type I collagen elastic fibers neural fibers vasa vasorum	Type I collagen elastic fibers neural fibers vasa vasorum	Type I collagen elastic fibers - -	Type I collagen elastic fibers - -	Type I collagen elastic fibers - -	- - - -